CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74-739

BIOEQUIVALENCE

3.1

Amiodarone Hydrochloride
200 mg Tablets
ANDA # 74-739
Reviewer: Andre J. Jackson
WP# 74739D.498

Copley Pharmaceutical
Canton, Ma.
Submission Date
April 7, 1998

Review of Dissolution Data

Background

The firm submitted a bioequivalence study for their amiodarone 200 mg tablet on August 31, 1995. The study was subequently amended on May 24, 1996 and was found to be acceptable. Since that submission the firm has changed the analytical method in the chemistry validation report. However the dissolution method which the firm used (the method is not a USP procedure) was the same as for the original submission. The chemistry reviewer told the firm that the dissolution study had to be repeated using the new analytical method and submitted to the Division of Bioequivalence for review.

Comment:

1.Since the dissolution method was not changed a new dissolution study is not required by the Division of Bioequivalence. Therefore, no further action will be taken related to this submission.

/S/

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG /S/
FT INITIALED YCHUANG /S/ Date: 7/21/98

Concur: _____ Date: 8/6/98
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Study Amendment (STA 20099 AC April 7, 98

SEP 13 1996

Amiodarone Hydrochloride Tablets	Copley Pharmaceutical
200 mg Tablets	Canton, MA
ANDA #74-739	Submission Date:
Reviewer: Moo Park	May 24, 1996
Filename: 74739a.596	

Review of an Amendment

I. Objectives

Review of Copley's amendment to a BE study comparing the bioavailability of Copley and Wyeth-Ayerst (Cordarone^{R}) 200 mg Amiodarone Hydrochloride Tablets following administration of a 400 mg dose in an open-label, randomized, 2-way crossover study under fasting conditions.

II. Comments

The firm was requested to respond to the two deficiencies shown below. Comments are shown following each deficiency as follows:

1. Conduct the comparative dissolution testing following the FDA method. (The firm was given the FDA method over telephone on 2/1/96.)

   Comment: The dissolution data are shown in Table 1. The dissolution data for the test product met the FDA specifications.

2. Submit the stability data for desethylamiodarone under long-term storage at -22°C.

   Comment: The long-term stability for desethylamiodarone is acceptable as shown in Table 2.

Table 2. Stability of Desethylamiodarone in Plasma

Sample, ng/mL	N	Storage Condition	Storage Time	%Initial	%CV
14.99	15	-22 °C	183 days	93.6	5.7
800.1	15	-22 °C	183 days	99.8	3.0

III. Recommendations

1. The bioequivalence study conducted under fasting conditions by Copley comparing its Amiodarone Hydrochloride Tablets, 200 mg, lot #133Z01 to Wyeth-Ayerst's Cordarone^{R}, 200 mg, lot #9940936, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Copley's Amiodarone Hydrochloride Tablets, 200 mg, is bioequivalent to Wyeth-Ayerst's Cordarone^{R}, 200 mg.

2. The dissolution testing conducted by Copley on its Amiodarone Hydrochloride Tablets, 200 mg, lot #133Z01, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of sodium acetate buffer at pH 5.0 containing at 37°C using USP 23 Apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

4. From the bioequivalence point of view the firm has met the *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 8/21/96

Concur: /S/ Date: 9/11/96

Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc:

Review history: Draft(8/16/96); Final (8/20/96)

Table 1. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Amiodarone Hydrochloride Tablets					
Strength	200 mg					
ANDA Number	74-739					
Applicant	Copley					
Reference Drug Product	Cordarone^{R} (Wyeth-Ayerst)					
II. USP Method for Dissolution Testing						
Medium and Volume	900 mL 0.022M sodium acetate buffer at pH 5.0 with 1% SLS					
Apparatus and rpm	paddle; 75 rpm					
Time	60 minutes					
Tolerances						
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No:133Z01 Strength:200 mg No of Units:12			Reference Product Lot No:9940936 Strength:200 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	81.3		7.9	82.2		7.2
30	87.0		7.2	87.3		6.4
45	89.4		5.5	92.1		2.7
60	90.4		4.9	92.2		2.5

Amiodarone Hydrochloride Tablets	Copley Pharmaceutical
200 mg Tablets	Canton, MA
ANDA #74-739	Submission Date:
Reviewer: Moo Park	August 31, 1995
Filename: 74739SD.895	

Review of a BE Study and Dissolution Data

I. Objectives

Review of Copley's BE study comparing the bioavailability of Copley and Wyeth-Ayerst (Cordarone^{R}) 200 mg Amiodarone Hydrochloride Tablets following administration of a 400 mg dose in an open-label, randomized, 2-way crossover study under fasting conditions.

II. Background

Amiodarone, a benzofuran, is a class III anti-arrhythmic drug (Vaughan Williams classification) indicated for the treatment of recurrent life-threatening ventricular fibrillation or hemodynamically unstable ventricular tachycardia. Amiodarone hydrochloride is a white to cream-colored crystalline powder. It is slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. It contains 37.3% iodine by weight.

Amiodarone hydrochloride should be used only when patients have not responded to adequate doses of other antiarrhythmics or when alternative agents cannot be tolerated. A uniform and optimal dosage schedule for amiodarone HCl has not been established. Generally, loading doses of 800 to 1600 mg per day are given in the hospital for 1 to 3 weeks with close electrocardiographic monitoring. Administration of amiodarone in divided doses with meals is suggested for total daily doses of 1,000 mg or higher, or when gastrointestinal intolerance occurs. Then daily doses of 600-800 mg are given (usually for 4 weeks) before maintenance treatment is started with 400-600 mg per day. Amiodarone is a highly toxic drug with therapeutic concentration range of about 1.0-2.5 mcg/ml; concentrations above this level are potentially toxic.

Amiodarone's oral bioavailability has been shown to vary from 20-80%, with an average of 50%. There is a large first-pass metabolism of amiodarone to mono-N-desethylamiodarone, which also possesses some antiarrhythmic activity. After absorption, amiodarone undergoes extensive enterohepatic circulation before being distributed to the central compartment and tissues. The volume of distribution is high (approximately 60 L/kg) because of

13 days after his scheduled dosing time in Period 2; Subject No. 26 withdrew 32.9 days prior to Period 2 dosing. Subject No. 12 was withdrawn from the study by the Medical Designate 27 minutes prior to Period 2 dosing due to medication that was taken for medical events. Thus a total of 35 subjects completed the crossover.

Subjects screening:

This study involved male volunteers, 18-35 years of age, weighing at least 60 kg, who are within 15% of their ideal weights (Table of Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983).

Medical histories and demographic data, including name, sex, age, race, body weight (kg), height (cm), body build and smoking habits were recorded. Each subject received a complete physical examination, chest x-ray (if not done in the last 3 months), 12-lead EKG and the laboratory tests of hematologic, hepatic and renal functions listed below. Only medically healthy subjects with clinically normal laboratory profiles and EKG's were enrolled in the study. Subjects must have FEV_1 values $\geq$80% of predicted normal values for their age, height, gender and race at screening and prior to each period.

Exclusions:

History or presence of significant:

- cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.

More specifically, history or presence of significant:

- eye disease in any form (except refractive disorders);
- lung disorder in any form, such as asthma or bronchitis;
- thyroid disorder in any form;
- liver disorder in any form;
- neurological disorder in any form;
- hypokalemia;
- bleeding disorder in any form;
- alcoholism or drug abuse within the last year;
- hypersensitivity or idiosyncratic reaction to amiodarone HCl or any other benzofurans;
- bradycardia and impairment of atrioventricular conduction;
- photosensitivity and skin disorders.

Subjects with sitting blood pressures of less than 110/70 mm Hg at screening or 100/60 mm Hg (90/55 mm Hg, supine) at the time of the pre-dose vital sign determination.

Subjects whose pulse is lower than 50 b.p.m. prior to dosing.

Subjects whose FEV_1 value <80% of predicted normal values for their age, height, gender and race at screening and prior to each period.

Subjects who have been on an abnormal diet (for whatever reason) during the four weeks preceding the study.

Subjects who, through completion of this study, would have donated in excess of 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in one year.

Subjects who have participated in another clinical trial within 28 days of study start.

Prohibitions:

No subject may take medication (including over-the-counter products) for the 7 days preceding the study. This restriction does not include daily vitamin supplements taken in non-therapeutic doses.

The consumption of alcohol- or xanthine-containing beverages and foods will be prohibited for 24 hours before dosing and throughout the period of sample collection.

If drug therapy other than that specified in the protocol is required during the time of sample collection, or during the washout period between drug administrations, a decision to continue or discontinue the subject will be made, based on the time the medication was administered and its pharmacology and pharmacokinetics.

8. Product information:

(a) Test product #1: Copley 200 mg Amiodarone Hydrochloride Tablets.

Lot #133Z01
Assay:97.6%
Content uniformity:99.9% (%CV=1.1)
Batch size: [illegible] Tablets

(b) Reference product: Wyeth-Ayerst Cordarone^R Tablets, 200 mg amiodarone hydrochloride.

Lot # 9940936
Assay:99.3%
Content uniformity:Not available
Expiration date: 7/97

9. Dosing: Single oral 400 mg (two tablets) amiodarone HCl dose,

administered with 240 mL of water.

10. Food and fluid intake: Subjects were required to fast overnight before dosing and for 4 hours thereafter. Water was permitted for 2 hours before and 4 hours after dosing, but were allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after dosing, and at appropriate times thereafter. During housing, meal plans were identical for both periods.

11. Housing: From 12 hours before dosing until after the 48 hour draw. Subjects returned for all subsequent blood draws.

12. Washout period: Eight weeks between doses.

13. Blood samples: Blood samples were collected in Vacutainers containing EDTA before dosing (1 x 10 mL) and at the following times after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, 48, 72, 96, 144, 240, 336, 504 and 672 hours (1 x 7 mL). For each volunteer, the total number of blood draws during the study were 40, and the total volume of blood drawn, including 25 mL for screening, and 15 mL for repeat tests, did not exceed 326 mL.

14. Urine samples: N/A

15. Subject monitoring: To monitor safety, sitting blood pressure and heart rate were measured before dosing and at the following times: 1, 2, 4, 6, 8, 12 and 24 hours after dosing. A 12-lead EKG was performed for each subject prior to dosing and at approximately 3, 6, 12 and 24 hours after dosing. All post-dose vital sign measurements were obtained within 8 minutes prior to the corresponding blood draws and the post-dose EKG's were performed within 46 minutes after their scheduled times. All EKG's were judged by the Medical Designate to be either within normal limits or not clinically significant. Vital signs and EKG's were performed at other times when deemed necessary. No safety problems were encountered.

16. IRB and informed consent: IRB approved the informed consent form.

17. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for log-transformed AUC_t, AUC_{inf} and C_{max}.

IV. Validation of Assay Method for Plasma Samples

Amiodarone and desethylamiodarone in plasma were assayed by using detection. Summary of the method is as follows:

Matrix: plasma
Anticoagulant:
Volume required: 500 mcL
Extraction method:
Internal standard:
Concentration range: amiodarone: 5.00-1000.0 ng/mL
desethylamiodarone:5.00-1000.0 ng/mL
Detection mode:
Quantitation: peak height ratio
Regression: linear
Weighting: 1/concentration

A. Pre-study validation

1. Specificity: No significant interference from endogenous components or other sources was observed.

2. Sensitivity: The lower limit of quantitation was set at 5.0 ng/mL for amiodarone and desethylamiodarone, respectively.

3. Linearity: Linear response over the concentration range of 5.0-1000.0 ng/mL for amiodarone and desethylamiodarone, respectively, was observed. The correlation coefficients were better than 0.999 for both analytes. Tables 1 and 2 show the back-calculated concentration data for the standard curve samples.

Table 1. Back-calculated Data for Standard Curve Samples
Amiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
5.01	3	4.811	96.0	3.6
10.26	3	10.57	103.0	1.5
50.07	3	48.80	97.5	1.2
151.84	3	160.9	106.0	2.1
500.67	3	474.9	94.9	1.8
751.01	3	770.7	102.6	0.5
902.85	3	918.8	101.8	2.6
1001.35	3	983.4	98.2	1.7

Table 2. Back-calculated Data for Standard Curve Samples
Desethylamiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
5.03	3	4.892	97.3	3.8
10.14	3	10.17	100.2	4.2
50.28	3	48.94	97.3	0.8
150.02	3	161.8	107.8	1.2
502.76	3	477.3	94.9	1.9
750.09	3	775.6	103.4	1.1
900.1	3	901.0	100.1	1.6
1001.47	3	990.3	98.9	1.5

4. Precision and accuracy: Tables 3-6 show the precision and accuracy data for the assay of QC samples. The precision and accuracy data are acceptable.

Table 3. Precision and Accuracy of QC Sample Assays
Amiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
14.99	6	14.70	98.1	4.0
401.0	6	393.3	98.1	1.0
800.1	6	792.3	99.0	2.9
5.02	6	5.195	103.5	8.8

Table 4. Precision and Accuracy of QC Sample Assays
Desethylamiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
14.99	6	13.29	88.7	6.1
401.0	6	382.9	95.5	3.4
800.1	6	787.4	98.4	1.5
5.02	6	5.273	105.0	10.0

Table 5. Within-batch Precision and Accuracy of QC Sample Assays
Amiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
14.99	10	14.77	98.5	4.2
401.0	14	389.7	97.2	0.8
800.1	10	813.0	101.6	0.9
5.02	10	5.147	102.5	5.3

Table 6. Within-batch Precision and Accuracy of QC Sample Assays Desethylamiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
14.99	10	12.70	98.3	3.7
401.0	14	368.8	84.7	1.3
800.1	10	790.3	92.0	2.5
5.02	9	4.937	98.3	5.3

5. Recovery: Tables 7-9 show the absolute recovery data for amiodarone, desethylamiodarone and internal standard , respectively.

Table 7. Absolute Recovery of Amiodarone in Plasma

Input, ng/mL	N	%Recovery	%CV
19.98	10	78.0	4.8
534.7	14	83.0	2.4
1066.7	10	91.8	3.7

Table 8. Absolute Recovery of Desethylamiodarone in Plasma

Input, ng/mL	N	%Recovery	%CV
19.98	10	69.5	4.4
534.7	14	85.4	2.5
1066.7	10	99.2	2.5

Table 9. Absolute Recovery of e in Plasma

Input, mcg/mL	N	%Recovery	%CV
2.67	30	87.3	2.8

6. Stability: Tables 10 and 11 summarize the stability data for amiodarone and desethylamiodarone in plasma, respectively. The long-term stability data for desethylamiodarone stored at -22 °C failed and were not reported. The firm stated that

these will be repeated.

Table 10. Stability of Amiodarone in Plasma

Sample, ng/mL	N	Storage Condition	Storage Time	%Initial	%CV
14.99	10	-22 °C	107 days	105.5	2.0
800.1	10	-22 °C	107 days	100.6	1.6
14.99	10	22 °C	5 hrs	99.4	1.8
800.1	10	22 °C	5 hrs	98.7	0.9
14.99	9	freeze-thaw	3 cycles	97.9	0.9
800.1	10	freeze-thaw	3 cycles	101.3	1.4
5.02	-	autoinjector 22 °C	18.4 hrs	99.9	-
14.99	-	autoinjector 22 °C	18.4 hrs	95.8	-
401.0	-	autoinjector 22 °C	18.4 hrs	99.9	-
800.1	-	autoinjector 22 °C	18.4 hrs	99.0	-
512.9 stock solution for standard	10	-22 °C	106 days	100.6	0.1
4999.3 stock solution for internal standard	9	-22 °C	109 days	95.5	0.2

Table 11. Stability of Desethylamiodarone in Plasma

Sample, ng/mL	N	Storage Condition	Storage Time	%Initial	%CV
Not reported		-22 °C			
Not reported		-22 °C			
14.99	10	22 °C	5 hrs	101.8	2.5
800.1	10	22 °C	5 hrs	100.8	1.1
14.99	10	freeze-thaw	3 cycles	102.2	2.0
800.1	9	freeze-thaw	3 cycles	97.4	0.7
5.02	-	autoinjector 22 °C	18.4 hrs	99.6	-
14.99	-	autoinjector 22 °C	18.4 hrs	104.1	-
401.0	-	autoinjector 22 °C	18.4 hrs	100.1	-
800.1	-	autoinjector 22 °C	18.4 hrs	103.4	-
506.8 stock solution for standard	9	-22 °C	106 days	106.6	0.2
4999.3 stock solution for internal standard	9	-22 °C	133 days	100.6	4.4

B. Within-study validation

1. Standard curve samples for the current study

Table 12. Back-calculated Data for Standard Curve Samples Amiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
4.99	22	4.817	96.5	5.7
9.97	23	9.989	100.2	3.4
49.85	22	48.90	98.1	2.1
149.6	23	159.9	106.9	2.6
498.5	23	486.5	97.6	2.2
747.8	23	752.9	100.7	2.6
899.4	22	898.9	99.9	1.5
997.1	23	995.2	99.8	1.9

Table 13. Back-calculated Data for Standard Curve Samples Desethylamiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
5.02	20	5.024	100.1	5.7
10.01	20	9.853	98.4	5.6
50.21	19	49.63	98.9	2.9
150.3	20	155.6	103.5	3.2
502.1	20	494.0	98.4	2.6
751.4	20	764.3	101.7	4.1
903.1	19	892.9	98.9	2.6
1000.8	20	1001.0	100.0	2.2

2. Precision and accuracy of quality control samples

Precision and accuracy for the QC samples are acceptable.

Table 14. Precision and Accuracy of QC Sample Assays
Amiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
15.0	44	13.75	91.6	5.8
398.3	45	391.3	98.2	2.4
797.1	42	801.8	100.6	2.2

Table 15. Precision and Accuracy of QC Sample Assays
Desethylamiodarone in Human Plasma

Input, ng/mL	N	Found, ng/mL	%Input	%CV
15.0	39	13.97	93.1	4.4
400.0	40	392.7	98.2	3.7
800.8	38	809.1	101.0	2.0

3. Repeat analyses: Seven samples were reassayed for amiodarone and 11 samples were reassayed for desethylamiodarone.

V. <u>In Vivo Results with Statistical Analysis</u>

This was an open-label, randomized, 2-way crossover study to compare the bioavailability of Copley and Wyeth-Ayerst (Cordarone^{R}) 200 mg amiodarone hydrochloride (HCl) tablets following administration of a 400 mg dose. A Single, oral 400 mg doses were separated by a washout period of 8 weeks.

Of the 40 healthy male volunteers enrolled in the study, five did not complete the crossover. The following subjects elected to withdraw from the study for personal reasons: Subject No. 16 withdrew 39.7 days prior to dosing in Period 2; Subject No. 19 withdrew approximately 24 days prior to Period 2 dosing; Subject No. 25 did not return for Period 2 and after being contacted by phone, withdrew approximately 13 days after his scheduled dosing time in Period 2; Subject No. 26 withdrew 32.9 days prior to Period 2 dosing. Subject No. 12 was withdrawn from the study by the Medical Designate 27 minutes prior to Period 2 dosing due to medication that was taken for medical events. Thus a total of 35 subjects completed the crossover.

Protocol Deviations: Contraventions of alcohol and xanthine prohibitions, strenuous activities, and deviations from the blood

sampling schedule were reported. The firm stated that the deviations reported were judged unlikely to affect the bioavailability comparison.

Medical Events: Subject #39 developed cramp in chest area 8 hours after dosing of the test product in Period 1. This was judged to be related to the drug/procedure and was not serious. The subject completed the crossover study.

The mean plasma levels and pharmacokinetic parameters are grouped separately under amiodarone and desethylamiodarone.

A. Amiodarone

1. Mean plasma levels

- Mean plasma levels for amiodarone for the test and reference products are comparable as shown in Table 16.

- Mean peak concentrations for the test and reference products are 277 ng/mL at 5 hours and 281 ng/mL at 6 hours, respectively.

Table 16. MEAN PLASMA AMIODARONE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	65.28	87.86	56.91	45.19	1.15
2	154.71	136.80	134.27	84.88	1.15
3	187.61	105.84	199.21	109.16	0.94
4	194.13	78.88	218.58	107.21	0.89
5	276.65	145.91	279.65	122.40	0.99
6	273.30	107.63	281.32	109.41	0.97
7	267.01	110.67	270.00	103.07	0.99
8	243.79	86.76	250.88	103.70	0.97
12	202.88	80.89	204.13	84.29	0.99
24	77.68	34.20	75.25	26.63	1.03
36	62.13	29.87	62.66	26.86	0.99
48	34.38	13.81	35.02	12.73	0.98
73	20.90	9.65	20.45	9.66	1.02
96	12.57	5.82	13.95	7.35	0.90
144	6.94	4.88	7.32	4.80	0.95
240	3.07	4.10	3.11	3.89	0.99
336	1.06	2.38	1.13	2.58	0.94
504	0.00	0.00	0.78	2.22	0.00
672	0.00	0.00	0.34	1.41	0.00

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST MEAN; MEAN2=REFERENCE MEAN; RMEAN12=TEST/REF RATIO

2. Pharmacokinetic parameters

- The pharmacokinetic parameters for the test and reference products are comparable. The test/reference ratios for non-transformed and log-transformed AUCT, AUCI AND CMAX are within a range of 0.96-1.02 as shown in Table 17.

- The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within 80-125% as shown in Table 18.

- The elimination half-life's for the test and reference products are 51 hours and 56 hours, respectively.

- There were significant period effects for non-transformed and log-transformed AUCT, AUCI AND CMAX. No sequence effect was detected.

Table 17. Summary of PK Parameters (*ANTILOG CONVERSION) For Amiodarone

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	8012.17	3532.52	7980.97	3868.00	1.00
AUCT	7514.57	3305.58	7807.46	3738.25	0.96
CMAX	304.92	151.89	299.39	120.80	1.02
KE	0.02	0.01	0.02	0.01	1.03
LAUCI*	7282.23	0.45	7216.72	0.45	1.01
LAUCT*	6831.04	0.45	7033.02	0.47	0.97
LCMAX*	277.15	0.43	278.00	0.39	1.00
THALF	51.48	28.77	55.91	45.06	0.92
TMAX	5.77	1.21	5.54	1.38	1.04

Table 18. LSMEANS and 90% Confidence Intervals for Amiodarone

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	8050.57	8069.96	88.16	111.36
AUCT	7549.25	7792.46	85.71	108.05
CMAX	306.29	299.04	88.22	116.63
LAUCI	7315.32	7314.43	90.55	110.47
LAUCT	6860.79	7018.02	88.54	107.94
LCMAX	278.15	277.67	90.22	111.22

B. Desethylamiodarone

1. Mean plasma levels

- Mean plasma levels for desethylamiodarone for the test and reference products are comparable as shown in Table 19.
- Mean peak concentrations for the test and reference products are 78 ng/mL at 12 hours and 78 ng/mL at 12 hours, respectively.

Table 19. MEAN PLASMA DESETHYLAMIODARONE LEVELS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1.26	2.83	1.77	2.92	0.71
2	10.52	7.19	10.47	8.15	1.00
3	20.60	10.90	21.46	11.79	0.96
4	28.16	12.06	30.41	13.33	0.93
5	50.21	16.54	52.65	15.71	0.95
6	55.25	17.86	60.31	16.10	0.92
7	63.08	17.69	66.56	17.29	0.95
8	67.40	18.91	69.92	18.59	0.96
12	78.33	23.58	78.17	21.17	1.00
24	65.62	18.04	67.19	15.38	0.98
36	66.50	19.46	68.60	16.39	0.97
48	57.59	17.54	58.84	14.45	0.98
73	49.43	15.51	49.47	12.21	1.00
96	42.45	12.44	43.60	12.30	0.97
144	33.51	10.81	35.32	9.91	0.95
240	24.76	8.23	24.90	6.87	0.99
336	17.83	5.84	18.32	5.50	0.97
504	10.80	3.64	11.28	3.88	0.96
672	6.84	3.42	6.62	4.30	1.03

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN1=TEST MEAN; MEAN2=REFERENCE MEAN; RMEAN12=TEST/REF RATIO

2. Pharmacokinetic parameters

- The pharmacokinetic parameters for the test and reference products are comparable. The test/reference ratios for non-transformed and log-transformed AUCT, AUCI AND CMAX are within a range of 0.97-0.98 as shown in Table 20.

- The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within 80-125% as shown in Table 21.

- The elimination half-life's for the test and reference products are 232 hours and 230 hours, respectively.

- There were significant period effects for non-transformed and log-transformed AUCT, AUCI AND CMAX. No sequence effect was detected.

Table 20. Summary of PK Parameters (*ANTILOG CONVERSION)
For Desethylamiodarone

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	18493.66	5011.66	19026.03	5455.55	0.97
AUCT	15818.23	4525.00	16074.63	4340.41	0.98
CMAX	79.28	22.66	81.08	19.52	0.98
KE	0.00	0.00	0.00	0.00	0.99
LAUCI*	17787.61	0.29	18294.36	0.28	0.97
LAUCT*	15128.61	0.31	15460.04	0.29	0.98
LCMAX*	76.08	0.30	78.52	0.27	0.97
THALF	231.63	56.62	230.26	60.71	1.01
TMAX	15.37	8.90	14.69	9.33	1.05

Table 21. LSMEANS and 90% Confidence Intervals

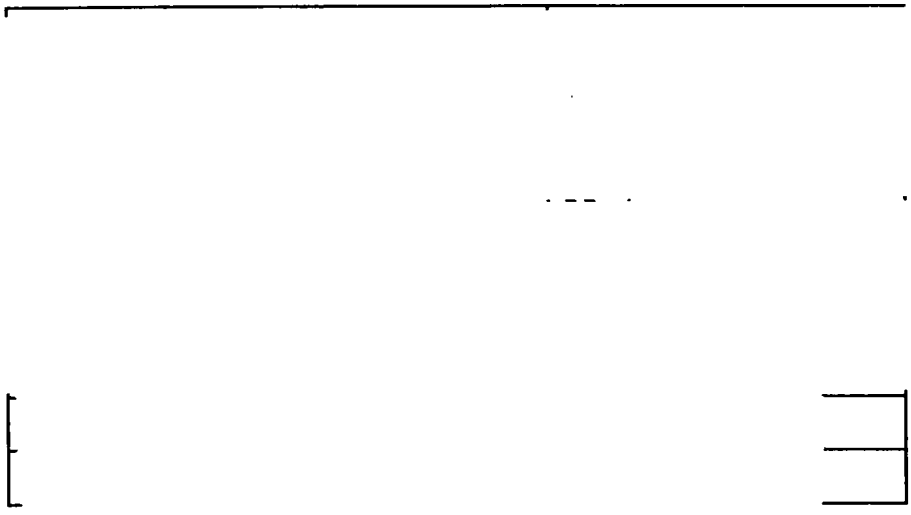
	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	18555.82	18981.02	91.85	103.67
AUCT	15871.33	16043.05	93.34	104.52
CMAX	79.45	80.97	91.54	104.70
LAUCI	17850.19	18253.82	92.32	103.58
LAUCT	15182.00	15426.58	92.25	104.99
LCMAX	76.22	78.40	90.69	104.25

VI. Product Information

1. Formulation

- The test and reference products contain qualitatively the same inactive ingredients besides the active ingredient.
- Test formulation is shown in Table 22.

Table 22. Test Formulation



2. Assay and content uniformity

Assay and content uniformity data for the test and reference products are summarized in Table 23.

Table 23. Assay and Content Uniformity Data

Product	Lot No.	Assay, %	Content Uniformity (%CV)
Test	133Z01	97.6	99.9 (1.1)
Reference exp:7/97	9940936	99.3	-

VII. Dissolution

Copley used its in-house method for the comparative dissolution study since USP 23 does not have the monograph for Amiodarone Hydrochloride Tablets. The dissolution data by the in-house method were summarized in Table 24.

However, Division of Bioequivalence recommends the following dissolution method:

Medium: 900 mL sodium acetate buffer at pH 5.0 containing 1% SLS

Apparatus 2: 75 rpm
Units: 12 units each product
Sampling times: 15, 30, 45, 60 minutes
Tolerance: .

VIII. Comments

1. This was an open-label, randomized, 2-way crossover study to compare the bioavailability of Copley and Wyeth-Ayerst (Cordarone^{R}) 200 mg amiodarone hydrochloride (HCl) tablets following administration of a 400 mg dose. A Single, oral 400 mg doses were separated by a washout period of 8 weeks.

   Of the 40 healthy male volunteers enrolled in the study, five did not complete the crossover. Data from the 35 subjects were used for the pharmacokinetic and statistical analyses.

2. The 90% confidence intervals for amiodarone and desethylamiodarone met the Agency criteria for bioequivalence:

A. Amiodarone

1. Mean plasma levels

- Mean plasma levels for amiodarone for the test and reference products are comparable.

- Mean peak concentrations for the test and reference products are 277 ng/mL at 5 hours and 281 ng/mL at 6 hours, respectively.

2. Pharmacokinetic parameters

- The pharmacokinetic parameters for the test and reference products are comparable. The test/reference ratios for non-transformed and log-transformed AUCT, AUCI AND CMAX are within a range of 0.96-1.02.

- The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within 80-125%.

- The elimination half-life's for the test and reference products are 51 hours and 56 hours, respectively.

- There were significant period effects for non-transformed and log-transformed AUCT, AUCI AND CMAX. No sequence effect was detected.

B. Desethylamiodarone

1. Mean plasma levels

- Mean plasma levels for desethylamiodarone for the test and reference products are comparable.

- Mean peak concentrations for the test and reference products are 78 ng/mL at 12 hours and 78 ng/mL at 12 hours, respectively.

2. Pharmacokinetic parameters

- The pharmacokinetic parameters for the test and reference products are comparable. The test/reference ratios for non-transformed and log-transformed AUCT, AUCI AND CMAX are within a range of 0.97-0.98.

- The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX are within 80-125%.

- The elimination half-life's for the test and reference products are 232 hours and 230 hours, respectively.

- There were significant period effects for non-transformed and log-transformed AUCT, AUCI AND CMAX. No sequence effect was detected.

3. Medical Events: Subject #39 developed cramp in chest area 8 hours after dosing of the test product in Period 1. This was judged to be related to the drug/procedure and was not serious. The subject completed the crossover study.

4. Assay method validation: Pre-study and within-study assay method validation for amiodarone and desethylamiodarone were acceptable except the stability data for desethylamiodarone under long-term storage at -22°C.

5. Batch size of the test product is ablets.

6. Assay and content uniformity data for the test and reference products are acceptable with the content uniformity data for the reference product not submitted. The firm is recommended to submit content uniformity data for reference product in future submissions.

7. Dissolution data by Copley's in-house method are not acceptable. The firm should conduct the comparative dissolution testing following the FDA method.

IX. Deficiencies

1. Conduct the comparative dissolution testing following the FDA method. (The firm was given the FDA method over telephone on 2/1/96.)

2. Submit the stability data for desethylamiodarone under long-term storage at -22°C.

X. Recommendation

The bioequivalence study conducted under fasting conditions by Copley comparing its Amiodarone Hydrochloride Tablets, 200 mg, lot #133Z01 to Wyeth-Ayerst's Cordarone^{R}, 200 mg, lot #9940936, has been found incomplete by the Division of Bioequivalence due to the deficiencies #1 and 2.

The firm should be informed of the recommendation and deficiencies #1 and 2.

/S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE /S/
FT INITIALED RMHATRE _____ 4/1/96

Concur: _____ Date: 2-12-96

Keith Chan, Ph.D. /S/
Director
Division of Bioequivalence

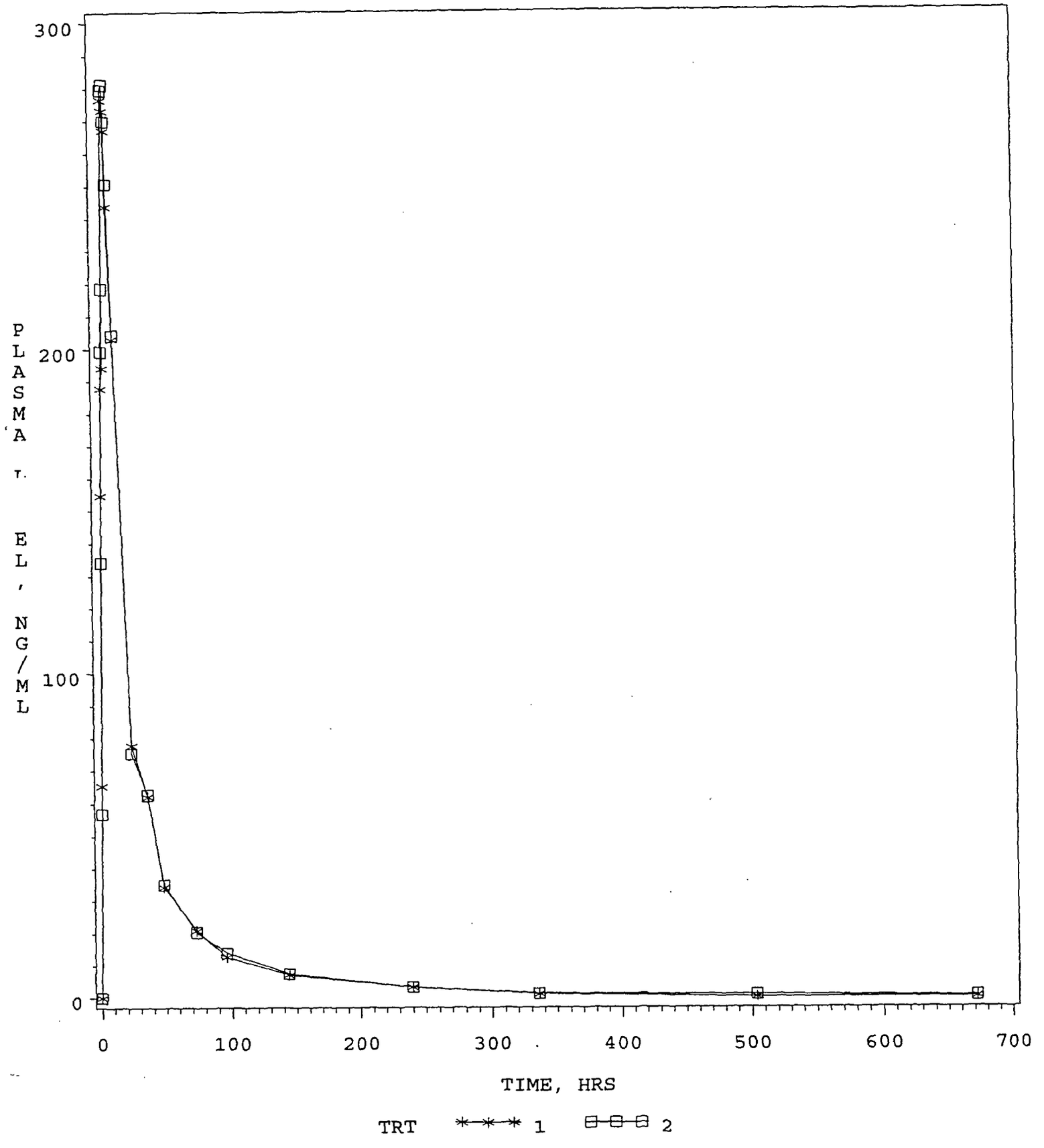
cc:

Review history: Draft(2/1/96); Final (2/7/96)

Table 24. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Amiodarone Hydrochloride Tablets					
Strength	200 mg					
ANDA Number	74-739					
Applicant	Copley					
Reference Drug Product	Cordarone^{R} (Wyeth-Ayerst)					
II. USP Method for Dissolution Testing						
Medium and Volume	900 mL 0.1 N HCl with 0.1% SLS					
Apparatus and rpm	paddle;100 rpm with capsule holders					
Time	60 minutes					
Tolerances						
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No:133Z01 Strength:200 mg No of Units:12			Reference Product Lot No:9940936 Strength:200 mg No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
10	79.6		7.9	89.9		3.7
20	88.7		8.8	94.1		2.6
30	90.9		6.9	94.7		2.7
45	92.9		4.6	94.9		2.7
60	93.8		3.9	95.1		2.3

FIG P-1. PLASMA AMIODARONE LEVELS

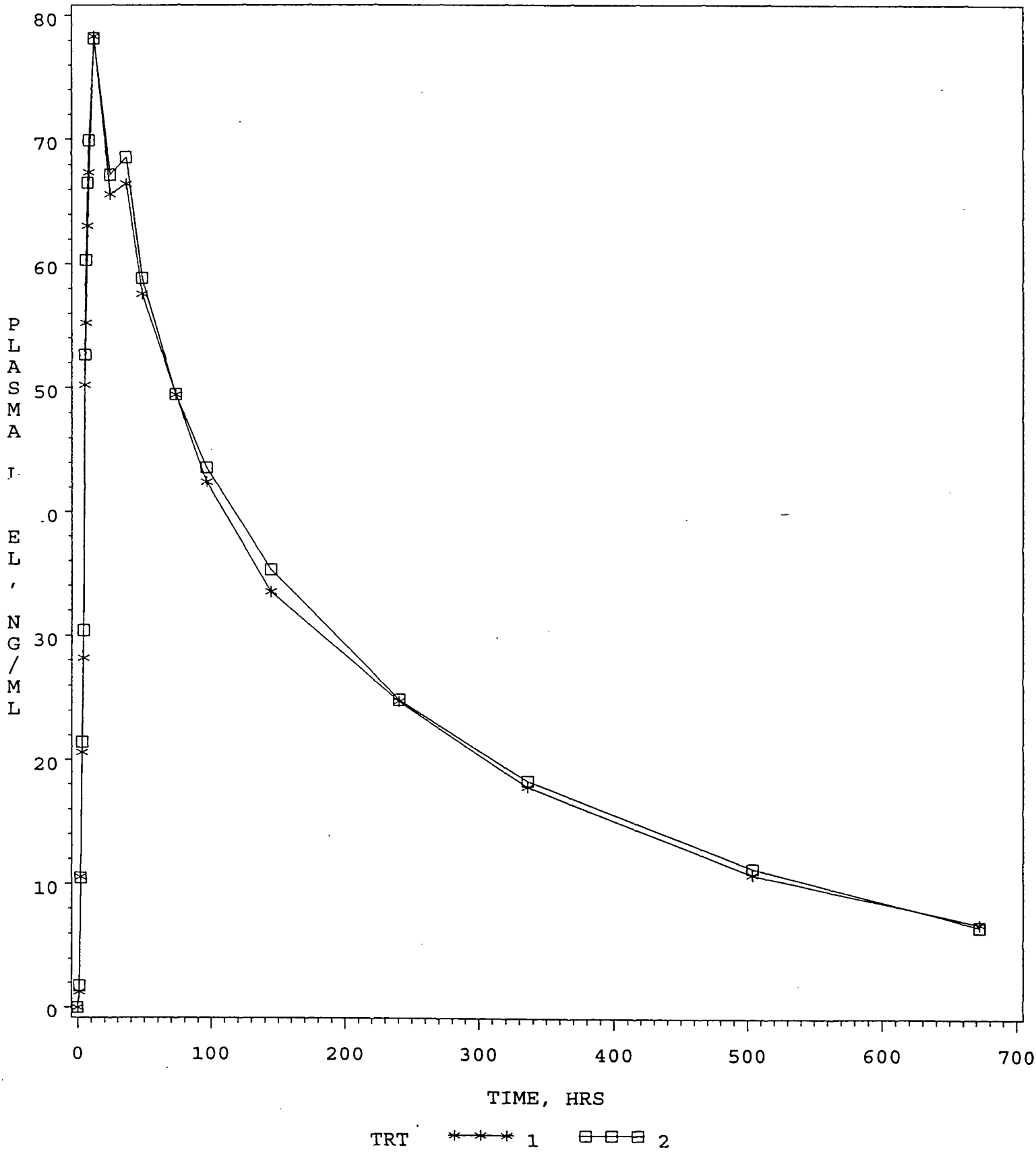
AMIODARONE HCL TABLETS, 200 MG, ANDA #74-739
UNDER FASTING CONDITIONS
DOSE=2 X 200 MG



1=TEST PRODUCT(COPLEY) 2=REFERENCE PRODUCT(WYETH-AYERST)

FIG P-2. PLASMA DESETHYLAMIODARONE LEVELS

AMIODARONE HCL TABLETS, 200 MG, ANDA #74-739
UNDER FASTING CONDITIONS
DOSE=2 X 200 MG



1=TEST PRODUCT(COPLEY) 2=REFERENCE PRODUCT(WYETH-AYERST)